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Amyotrophic lateral sclerosis: a higher than expected incidence in people over 80 years

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Abstract

Objective: To determine the age-specific incidence and clinical-epidemiological characteristics of an Amyotrophic lateral sclerosis (ALS) cohort patient in Catalonia (Spain). **Methods and results:** New cases diagnosed between January 1, 2004 and December 31, 2013 were 41 (20 men and 21 women), with an annual crude incidence rate of 2.7 per 100,000 person-years (95% CI 1.90 – 3.59). The incidence rate increased with age reaching a peak in the age-group of 70 to 79 years. There was a non significant decrease in the incidence rate in the group of patients over 80 (P value = 0.75) 17.99 per 100 000 person years (95% CI 7.81 – 28.17). The percentage of patients over age 80 was 29.3% and over age 85 was 9.8%. The prevalence rate at the end of the study period was 8.38/100.000 of the total population. Mean age at symptom onset was 76.0 years. Onset of symptoms was bulbar or generalized in 36.6% of cases.

Conclusions: ALS incidence in Osona is within the range of other countries across Europe. Our results suggest that the age-specific incidence rate of ALS increases with age through the oldest age groups suggesting an age-risk effect to develop the disease.

Introduction

Amyotrophic lateral sclerosis (ALS) is a relatively uncommon neurodegenerative disorder of unknown aetiology. The disease affects upper and lower motor neurons causing rapidly progressive paralysis leading to death due to respiratory failure usually within 3 years from symptom onset.

Because of the low frequency and short survival of people with ALS, large numbers of well characterized patients from homogeneous populations within defined geographical areas are required to provide detailed epidemiological data to achieve conclusions. Prospective, population-based methodology has been shown to be useful in defining clinical characteristics and prognostic indicators. Reported incidence rates are remarkably uniform across all registries among Caucasian populations, ranging from 1.7 to 2.3 cases per 100 000 person-years¹⁻³.

However, several important epidemiological questions remain unsolved. The evidence suggests that ALS risk is probably an age-related condition with a variable

pattern of susceptibility and a higher risk within a susceptible age group in the late sixties or early seventies. Most population-based studies report that the incidence of ALS increases with age, reaching a peak around 70 years old but is then followed by a decline in frequency in those over 80 years. The whole data suggest that susceptibility is lower among the subpopulation of the very elderly^{1,4-8}. However, whether the age-specific incidence of ALS increases over time through the oldest age groups suggesting an age-risk effect, or the incidence decreases among the very elderly remains an open question³.

The decline of incidence rates in those over 75 years has been attributed to difficulties with case ascertainment among this particularly fragile group of patients. Several reasons have been put forward, such as difficulty in diagnosing ALS among the elderly because of comorbidity, difficulty in access to specialised care or a more rapid and aggressive disease and shorter survival that cause elderly patients to die before the diagnosis of ALS is established^{3,7,9,10}. Identification of subpopulations at risk is likely to help to our understanding of the disease pathogenesis.

With the hypothesis of underdiagnosis of ALS among older people, and to counteract the problems in diagnosis in the older age groups, we set up a population register of ALS patients using multiple sources of information and prospective ascertainment of cases within a very small catchment area. The national health system in Catalonia allows free access to medical care meaning that most cases with a suspected ALS are assisted by a neurologist at some stage of the disease.

Methodology

Study area and study population

The study was conducted in the county of Osona in Central Catalonia, Spain. The population of the study area was of 138,630 inhabitants and increased up to 155,069 during the study period between January 2004 and December 2013 according to national census data¹¹. Individuals under the age of 18 were excluded to avoid misclassification. Patients were eligible when resident in the study area at least 2 years before the date of the diagnosis.

Case ascertainment

The Vic University Hospital is the referral centre of the National Health System which covers the total population of the study area. The main source of cases was an

ongoing prospective hospital registry of ALS patients. The registry was set up in 2004, and case collection began in January 2004. In addition, we used several sources of information to obtain a complete case ascertainment. All neurologists working in the public health system, including local hospital and in the ambulatory consultation, within the study area were involved in the registry. Rehabilitation and geriatrics departments were also contacted and asked to report all possible cases. General practitioners have also been invited to ascertain patients with ALS. They have been adequately assessed and have received support. One of the neurologist involved in the study periodically attended meetings with health care professionals working in primary care and the Geriatrics in the study area to discuss and review cases with uncertain diagnosis. Archives of the ALS patients' association were reviewed and ALS experts working in regions adjacent and tertiary referral centres and neurologists working in private centres were invited to participate in the study.

Diagnostic criteria

The diagnosis of ALS was based on the revised version of The El Escorial Criteria¹². Patients with all forms of motor neuron disease were included, but only subjects with criteria for definite, probable or possible ALS were included for the analysis of incidence and prevalence data. Patients with progressive muscular atrophy and primary lateral sclerosis variants who did not fulfil criteria for ALS during follow up were excluded from the analysis. Patients were diagnosed by a consultant neurologist. All patients underwent one or more electrophysiological studies; the results were reviewed to ensure a clinical diagnosis of ALS. We defined probable familial ALS (fALS) when one affected first- or second-degree relative was identified¹³.

Data management

A standard form was used to prospectively collect patients' demographic and clinical data and register all eligible patients according to the study protocol. Records included place of residence, sex, date of onset and age at time of symptom onset, date of diagnosis, and site of onset, recorded as spinal or bulbar. Delay in diagnosis (the period of time between onset and diagnosis) and median time of survival from onset of the disease were both recorded in months. All the data were submitted and anonymized for data analysis to a central office at the Neurology Department of the Vic University Hospital. Death certificates of patients with ALS were provided by the Health

Department of the Government of Catalonia. The study was approved by the Clinical research and ethics committee of Vic Hospital Consortium.

Data analysis

The prevalence rate was estimated on December 31, 2013 using the number of patients with an ALS diagnosis. The denominator for the calculation of prevalence rates was the Osona county population in 2013.

Incidence rates were calculated for the entire study population, for specific age groups and by sex. The population of the catchment area older than 18 years was considered to be at risk of developing ALS. Age and gender specific incidence rates for the study population were calculated from the numbers of new cases identified, divided by the combined age and gender specific person-years of observation estimated from census data for the geographical region during the period 2004-2013. Crude and standardized incidence rates were adjusted using the European population (OMS¹²) at the same period using the direct method OMS¹⁴. Ninety-five percent confidence limits were calculated assuming a Poisson distribution. For the analysis a P value < 0.05 (two-sided) was considered statistically significant.

Descriptive analyses were performed. Categorical variables were described by frequencies and percentages. Continuous variables were described by means and standard deviations. Relationships between categorical variables were studied using the χ^2 test and *Yates test*, and continuous variables were analyzed using Student's *t-test*. The Kaplan-Meier product limit distribution was used for survival analysis. All analyses were performed with SPSS for windows *Statistics 21*.

Results

During the study period, between 1 January 2004 and 31 December 2013, 41 new cases, 20 males (48.8%) and 21 females (51.2%) were diagnosed with ALS. Thirteen patients were alive on 31 December 2013, giving a point prevalence of 8.38 cases per 100,000 of the total population. Mean age at symptom onset was 76.0 years for the whole population, ranging from 42 to 89 years, 77.50 years for males and 71.19 years for females. Onset of symptoms was bulbar in 36.6% of cases with no significant differences by age (P value = 0.77) and gender (P value = 0.84). The mean time delay from onset to diagnosis was 10.74 ± 6.52 months, shorter in bulbar onset. There were no significant differences (P value = 0.75) in the mean time delay to diagnosis between patients older than 80 years (1.58 ± 5.23 months) and younger than 80 years (10.81 ± 7.08 months).

Ten patients coming from the study area were identified during the study period in the registers of the two referral centres for ALS involved in the study. All of them have been previously registered within the study area and attended the specialized Units looking for an expert opinion on diagnosis. Familial cases represented 7.5% of cases. All three fALS cases were in the 70-79 years age group. According to the El Escorial revised criteria we classified 90% of cases as definite and 10% as probable ALS. Five patients with progressive muscular atrophy and one with primary lateral sclerosis variants were excluded.

The overall annual crude incidence rate was 2.74 per 100 000 person-years (95% CI 1.90 – 3.59). The incidence rate in males was 2.67 (95% CI 1.50 – 3.84) and in females 2.82 (95% CI 1.61 – 4.03), with a ratio of 0.95. Mean annual incidence adjusted by age and gender to the European population was 3.08 (95% CI 2.00 – 4.17). The age-specific incidence rates of by gender are illustrated in figure 1. The incidence rate of ALS increased markedly with increasing age, from none in those aged under 30 to 0.30 per 100 000 person years (95% IC 0.0 – 1.15) in the age group of 30 to 59 years and to 4.73 per 100 000 person years (95% IC 1.04 – 8.43) in the age group of 60 a 69 years, reaching 18.22 per 100 000 person years (95% IC 11.17 – 25.27) in the age group of 70 to 79 years. There was a non significant decrease in the incidence rate in the group of patients over 80 (P value = 0.75) 17.99 per 100 000 person years (95% CI 7.81 – 28.17) (Table 1). The percentage of patients over age 80 was 29.3% and over age 85 was 9.8%.

Mean survival time from symptom onset by Kaplan-Meier analysis was 26.62 ± 3.06 months. There were no gender differences (P value = 0.77) between males (26.43 ± 4.67 months) and females (26.70 ± 4.12 months). Mean survival time by age group was 30.91 ± 3.90 months for patients younger than 80 years, significantly longer (P value = 0.0009) than for the group of patients older than 80 years (16.83 ± 3.18 months). There was no significant difference (P value = 0.88) in mean survival time between spinal (27.64 ± 3.89) onset forms and bulbar onset forms (24.80 ± 5.25).

Median survival time from symptom onset was 19.15 ± 3.07 months. Median survival time from diagnosis was 9.48 months.

Discussion

We have conducted a prospective, population-based epidemiological study of ALS over a period of 10 years within a small county of Barcelona province, Catalonia,

Spain, comprising a very stable population. The ultimate objective of the study was to determine if the age-specific incidence of ALS increases with age through the oldest age groups. The study was carried out within a small, well-defined and restricted geographical area with only one referral hospital, during a long time period and using secondary sources of case ascertainment to maximise case ascertainment and balance the small sample size.

Our observed incidence rates are within the range of most other previous population-based studies using population-based methodology³. We found that incidence rates continue to increase with age and the elderly contributed substantially to the frequency of ALS; the percentage of patients over age 75 was 55%, being 29.3% over age 80 and 9.8% over age 85.

The body of literature on ALS epidemiology is large but limited geographically¹⁵. Most research has been conducted in Europe¹⁵.

Our incidence rates are slightly higher than those found in a population-based study carried out in the whole territory of Catalonia including the geographical area where our study was performed¹⁶. Comparison of incidence of the two studies in the people younger than 60 years is difficult because of the extremely low number of cases. The differences in the overall annual incidence rates among the two studies can be attributed to the higher incidence rates in the subgroups of patients over 70 years and are clearly different in the very elderly subgroup of patients aged 80 and over. These differences are probably a consequence of the procedures and methods used to improve patient capture among elderly onset cases, and the multiple sources of case ascertainment used.

Previous studies have included only a small number of patients over the age of 80 years. A meta-analysis of published population based registries completed in three European countries specifically addressed the need to study age-specific incidences over time to distinguish if ALS is a disease of ageing or if there is a decrease in incidence among the very elderly³. In that study, incidence rates for the combined European cohort increased with advancing age, reaching a peak in the late sixties or early seventies, followed by a rapid decline, with 6.6% of patients over age 80 and only 1.9% over 85 years³. This pattern seems to be consistent across the four published European registries^{10,15}. The analysis generated a large number of ALS patients within this age group and allowed the authors to conclude there was a true decrease in incidence rates among the oldest groups of patients. However, the decrease in incidence rates in the population over 75 years of age might in fact still be a result of

under-ascertainment. Most population based studies show a peak of incidence in the 65-75 age-group¹⁵, only in two studies incidence rates are maintained in the age-group over 80 years^{2,24}.

When large populations are analyzed some cases, such as those patients in extreme age groups, can be missed, and the analysis of incidence rates by age might be imprecise. A weakness of the study is the small size of the study population, but it is extremely stable and has very clearly defined boundaries of the catchment area, allowing precise capture of cases¹⁷. The study was conducted within a geographical area with only one reference hospital, in a national health system which provides free access to medical care. Furthermore, the referring physicians have a close working relationship with each other, increasing referral rates to the register. This setting allowed us to undertake very close surveillance of all incident cases. Using the same approach in the same geographical area, we have studied the incidence of other neurologic disorders and found the highest reported incidence of myasthenia gravis in the elderly¹⁸.

Previous studies have found that fewer than 10% of patients with ALS experienced symptom onset over the age of 80 and ALS has been considered exceptional over age 85. Only two previous studies have found a proportion of cases of people over 80 years above 10%^{2,24}. For example, a recent study in the Limousin region in France found higher incidences in the oldest age groups, where ALS incidence showed a progressive rise with age culminating in a large peak between 65 and 85 years¹⁹. Although we cannot extrapolate our findings to other populations, when taken together with the results from Limousin they suggest that ALS risk may truly increase with age, and an increasing incidence will reflect the ageing of populations in western countries. Table 2 shows a comparison of age specific incidence rates between elderly in Europe.

The proportion of patients with bulbar-onset ALS in our study (36.6%) was higher than the result of the combined analysis of the epidemiological data collected from six European ALS registers (30.01%)¹. The percentage of bulbar-onset patients is also most common than the reported in other studies^{2,3,11,12,14}. As bulbar-onset ALS may be more common in the oldest age groups, this difference may be explained by the higher proportion of elderly patients in our population.

Our data supports the notion that motor neuron degeneration may be an inevitable part of the ageing process. However, conclusions of the study should be considered cautiously because the low numbers of cases registered in our study.

Previously reported low incidence rates among patients in older age-groups may be explained by misdiagnosis of the disease in the group of very old patients. A close working relationship and educational interventions among health care professionals in primary care service may help to identify patients with suspected motor neuron disease and to improve case ascertainment in elderly onset cases. This hypothesis needs to be explored and confirmed in future epidemiological studies with larger populations.

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Table 1.

Age and gender specific incidence of ALS per 100,000 person-years among those aged 18 years and over, from the Osona ALS register for the 10 year period 2004-2013.

Age group	Men				Women				Total			
	Cases	Person-years*	Incidence**	95% CI	Cases	Person-years*	Incidence**	95% CI	Cases	Person-years*	Incidence**	95% CI
18-19	0	15369	0.0	0.0-	0	14445	0.0	0.0-0.0	0	29814	0.0	0.0-0.0
20-29	0	100385	0.0	0.0-	0	95729	0.0	0.0-0.0	0	196114	0.0	0.0-0.0
30-39	0	133541	0.0	0.0-	0	117024	0.0	0.0-0.0	0	250565	0.0	0.0-0.0
40-49	0	120147	0.0	0.0-	2	110178	1.8	1.7-1.9	2	230325	0.9	0.8-0.9
50-59	0	93030	0.0	0.0-	0	89262	0.0	0.0-0.0	0	182292	0.0	0.0-0.0
60-69	1	61211	1.6	1.6-	5	65606	7.6	7.4-7.8	6	126817	4.7	4.6-4.9
70-79	12	50197	23.9	23.5-	9	65052	13.8	13.6-	21	115249	18.2	18.0-
80-89	7	24929	28.1	23.5-	5	41776	12.0	11.7-	12	66705	18.0	16.2-
Total***	20	749.162	2.7	1.5-	21	744.643	2.8	1.6-4.0	41	1.493.805	2,7	1.9-3.6

Foot legend table 1

* Osona population 2004-2013

** Per 100,000 person-years

*** Total population.

Table 2. Comparison of age specific incidence rates between elderly in Europe.

Region	Years	Crude incidence x 100.000	75-79 years	80-84 years	≥85 years
Puglia (Italy) ¹	1998- 1999	1.6			0
Scotland ²	1989- 1998	2.4	11.3 (9.6- 13.3)	9.9 (3.2- 7.1)	
EURALS (Europe) ³	1998- 1999	2.16	8.0 (6.7- 9.4)	5.2 (3.7- 6.6)	2.5 (1.4- 3.5)
Catalonia ¹⁶	1999- 2001	1.4	4.7 (3.1- 6.3)	2.2 (0.8- 3.7)	0.9 (0-2.8)
Limousin ¹⁹	2000- 2011	3.2 (2.8- 3.6)	11.5		
South-East England ²⁰	2002- 2006	1.06	Males 0.9; Females 2.2	Males 1.4; Females 1.2	Males 2.1; Females 0.8
Friuli Venezia Giulia ²¹	2002- 2009	2.72			3.6 (1.3- 6.0)
Sardinia ²²	2005- 2009	2.5			0
Rhineland- Palatinate ²³	2010- 2011	1.8	2.8 (1.3- 5.3)	4.5 (2.3- 8.0)	0.5 (0-2.7)
Modena ²⁴	2000- 2009	2.9	9.4		
Osona	2004- 2013	2.74	19.1 (7.8- 30.4)	18.4 (5.7- 31.2)	11.8 (2.4- 23.4)

Figure 1.

Age-specific incidence rates by gender in the county of Osona in Central Catalonia, Spain (January 2004 and December 2013).

